BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-32559/84
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 570067

(54) Title
CHROMANYLALKOXYBENZYL SUBSTITUTED THIAZOLIDINES

(51)4 International Patent Classification
C07D 417/12 C07D 417/14

(21) Application No. : 32559/84 (22) Application Date : 30.08.84

(30) Priority Data

(31) Number (32) Date (33) Country
58-158375 30.08.83 JP JAPAN

(43) Publication Date : 07.03.85

(44) Publication Date of Accepted Application : 03.03.88

(71) Applicant
SANKYO CO. LTD.;

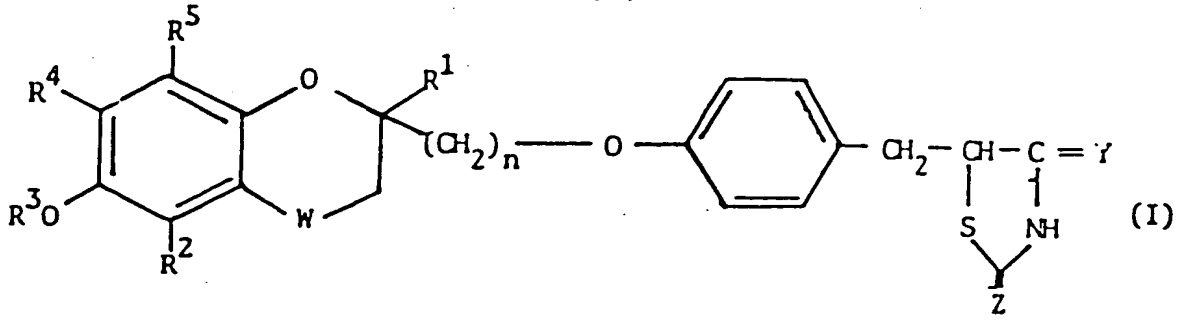
(72) Inventor
TAKAO YOSHIOKA
EIICHI KITAZAWA
TOMOYUKI KARUMADA
MITSUO YAMAZAKI
KAZUO HASEGAWA

(74) Attorney or Agent
GRIFFITH, HASSEL & FRAZER

(56) Prior Art Documents
24601/84 C07D 493/04

(57) Claim

1. Compounds of formula (I):



(I)

[in which:
R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group;
R^3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group in which the heterocylic moiety thereof has one or more oxygen, sulphur or nitrogen hetero atoms and has from four to seven ring atoms, an araliphatic acyl group, a (C_1-C_6 alkoxy)carbonyl group or an aralkyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, or R^4 and R^5 together represent a C_1-C_4 alkylenedioxy group;
n is 1, 2 or 3;
W represents the $-CH_2-$, >CO or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and
Y and Z are the same or different and each represents an oxygen atom or an imino group]
and pharmaceutically acceptable salts thereof.

17. A pharmaceutical composition for the treatment of hyperlipaemia or hyperglycaemia, which comprises at least one active compound in admixture with a pharmaceutically acceptable carrier or diluent, wherein said active compound is at least one compound as claimed in any one of the preceding Claims.

M&C FOLIO: 48329 WANGDOC: 0160H

THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

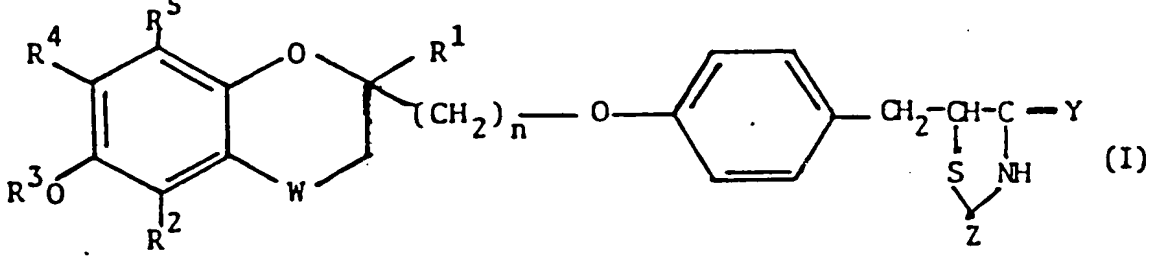
The present invention relates to a series of new thiazolidine derivatives, which we have found to have a variety of valuable biological activities, coupled with an exceedingly low toxicity. The invention also provides processes for preparing the compounds and pharmaceutical compositions containing them.

A number of thiazolidine derivatives are disclosed in European Patent Publication No. 8203 and in Chem. Pharm. Bull., 30, 3580 (1982). Certain of the thiazolidine derivatives disclosed in these documents have the ability to lower blood lipid and blood sugar levels, although these compounds are a little toxic.

We have now discovered a series of new thiazolidine derivatives which likewise have the ability to lower blood lipid and blood sugar levels and, in addition, have a number of other valuable activities, but which have very low toxicity. In general, the compounds of the invention show blood lipid metabolism ameliorating

activity. Specifically, the compounds have the ability to decrease the levels of blood lipid peroxides, blood triglycerides and blood cholesterol.

The compounds of the present invention are compounds of formula (I):



(I)

[in which:

R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group;

R^3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group in which the heterocyclic moiety thereof has one or more oxygen, sulphur or nitrogen hetero atoms and has from four to seven ring atoms, an araliphatic acyl group, a (C_1-C_6 alkoxy)carbonyl group or an aralkyloxycarbonyl group;

R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxy group, or R^4 and R^5 together represent a C_1-C_4 alkylenedioxy group;

n is 1, 2 or 3;

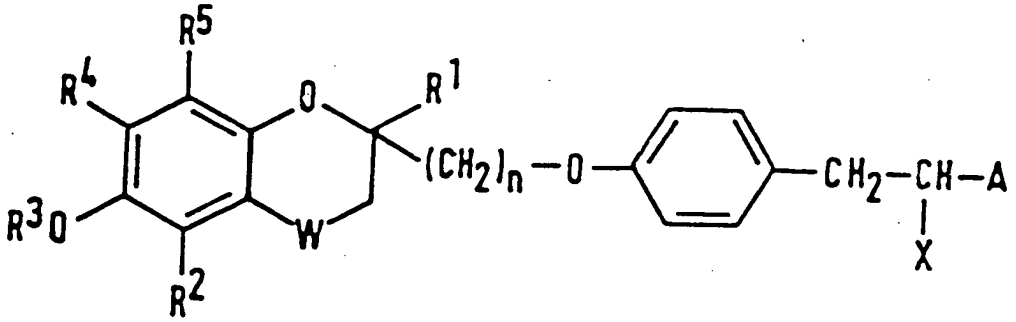
W represents the $-CH_2-$, >CO or $>CH-OR^6$ group (in which R^6 represents any one of the atoms or groups defined for R^3 and may be the same as or different from R^3); and

Y and Z are the same or different and each represents an oxygen atom or an imino (=NH) group]

and pharmaceutically acceptable salts thereof.

The invention also provides a process for preparing the compounds of the invention by:

(a) reacting a halopropionic acid derivative of formula (II):



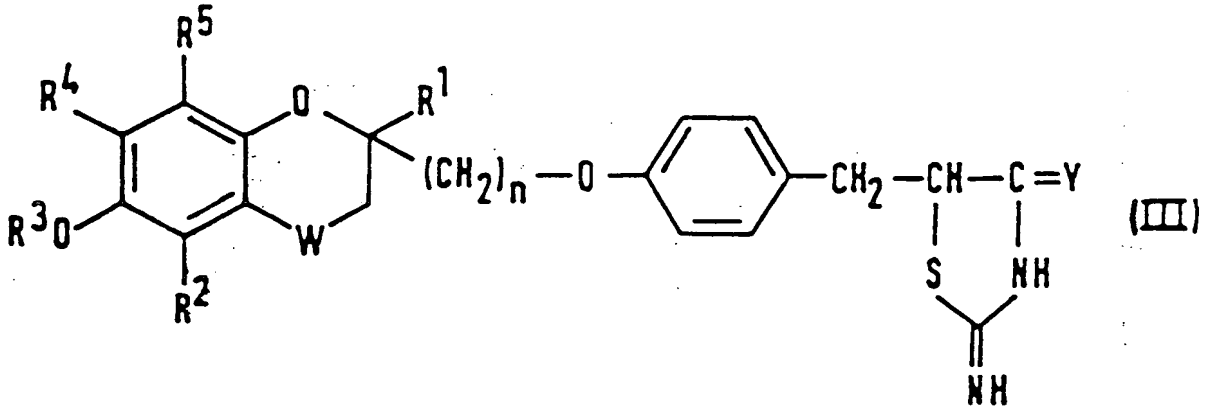
(II)

[in which:
R^1, R^2, R^3, R^4, R^5, n and W are as defined above;

X represents a halogen atom; and

A represents a cyano group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group or a group of formula $-COO(M)_m$, in which M represents a cation and m represents the reciprocal of the valency of the cation M]

with thiourea, to give a compound of formula (III):



(III)

(in which R^1, R^2, R^3, R^4, R^5, n, W and Y are as defined above) and then,

(b) if necessary, subjecting said compound to hydrolysis (which may be selective) to prepare said compound of formula (I).

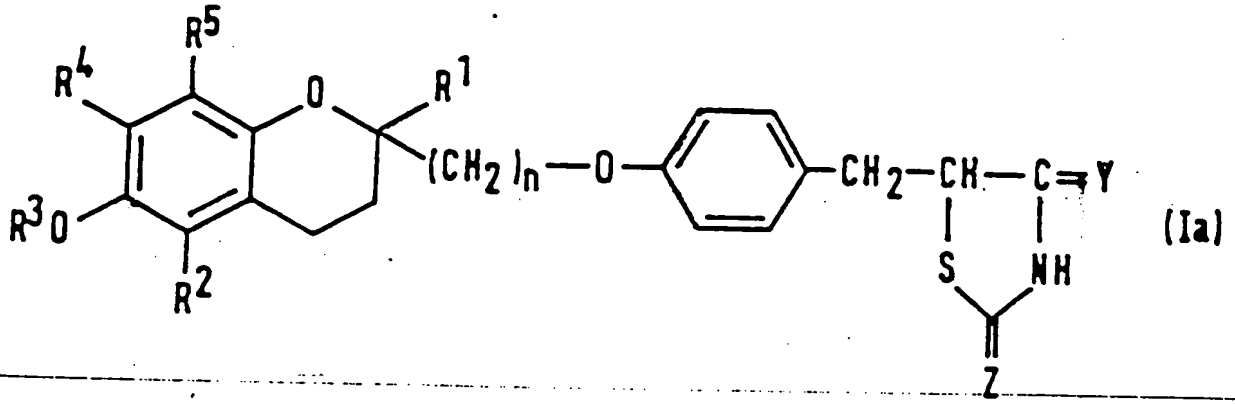
(c) optionally, where W represents a >C=O group, reducing the compound produced in step (a) or step (b) to a compound where W represents a >CH-OH group,

(d) optionally, where W represents a >CH-OH group, acylating the compound to give a compound in which W represents a group of formula $>CH-OR^{6'}$ (in which $R^{6'}$ represents any of the groups defined for R^6 but not the hydrogen atom), and

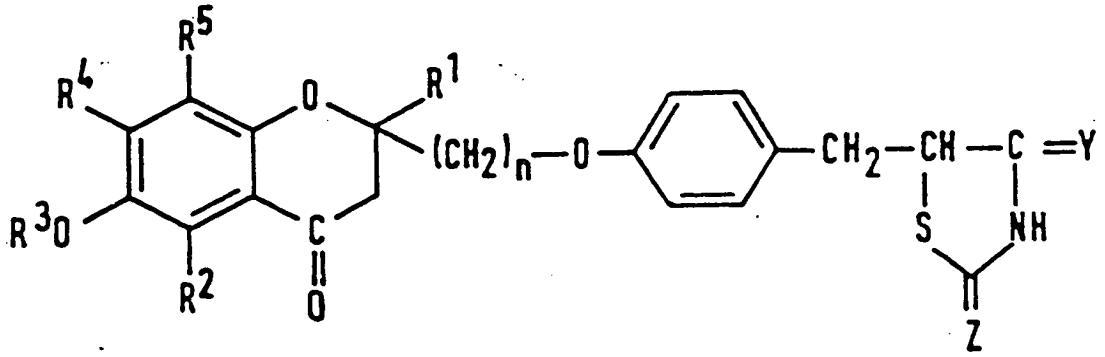
(e) if necessary, salifying the product.

The invention also provides a pharmaceutical composition for the treatment of hyperlipaemia or hyperglycaemia, which comprises at least one compound of the invention in admixture with a pharmaceutically acceptable carrier or diluent.

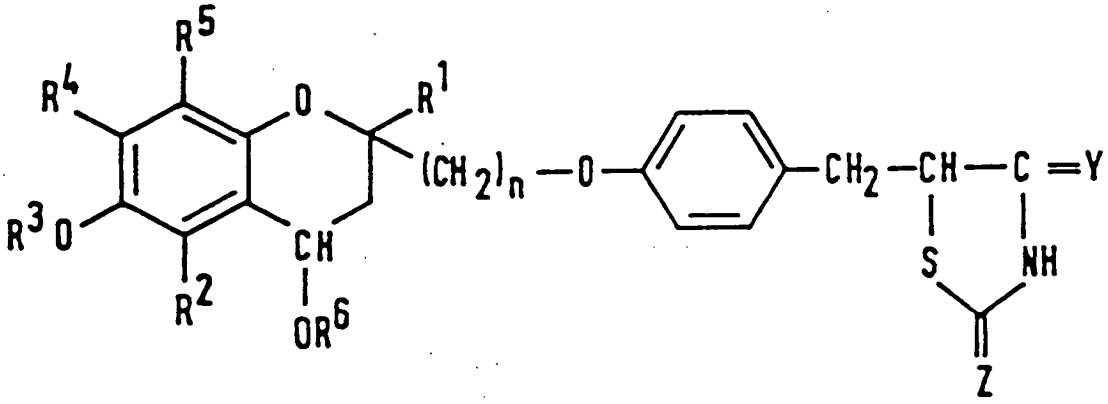
The compounds of the invention, which are 5-[4-(chromanalkoxy)benzyl]thiazolidine derivatives, may be represented by the formulae (Ia), (Ib) and (Ic):



(Ia)



(Ib)



(Ic)

(in which R^1, R^2, R^3, R^4, R^5, R^6, n, Y and Z are as defined above) and include pharmaceutically acceptable salts thereof.

In the compounds of the invention, where R^1 or R^2 represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 5 carbon atoms and is preferably a primary or secondary alkyl group, for example the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl or isopentyl group.

Where R^3, R^6 or $R^{6'}$ represents an aliphatic acyl group, this preferably has from 1 to 6 carbon atoms and may include one or more carbon-carbon double or triple bonds. Examples of such groups include the formyl, acetyl, propionyl, butyryl, isobutyryl, pivaloyl, hexanoyl, acryloyl, methacryloyl and crotonoyl groups. Where R^3, R^6 or $R^{6'}$ represents an alicyclic acyl group, it is preferably a cyclopentanecarbonyl, cyclohexanecarbonyl or cycloheptanecarbonyl group. Where R^3, R^6 or $R^{6'}$ represents an aromatic acyl group, the aromatic moiety thereof may optionally have one or more substituents (for example nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents); examples of such aromatic acyl groups include the benzoyl, p-nitrobenzoyl, m-fluorobenzoyl, o-chlorobenzoyl, p-aminobenzoyl, m-(dimethylamino)benzoyl, o-methoxybenzoyl, 3,4-dichlorobenzoyl, 3,5-di-t-butyl-4-hydroxybenzoyl and 1-naphthoyl groups. Where R^3, R^6 or $R^{6'}$ represents a heterocyclic acyl group, the heterocyclic moiety thereof preferably has one or more, preferably one, oxygen, sulphur or nitrogen hetero atoms and has from 4 to 7 ring atoms; examples of such heterocyclic acyl groups include the 2-furoyl, 3-thenoyl, 3-pyridinecarbonyl (nicotinoyl) and 4-pyridinecarbonyl groups. Where R^3, R^6 or $R^{6'}$ represents an araliphatic acyl group, the aliphatic

moiety thereof may optionally have one or more carbon-carbon double or triple bonds and the aryl moiety thereof may optionally have one or more substituents (for example nitro, amino, alkylamino, dialkylamino, alkoxy, halo, alkyl or hydroxy substituents); examples of such araliphatic acyl groups include the phenylacetyl, p-chlorophenylacetyl, phenylpropionyl and cinnamoyl groups. Where R^3, R^6 or $R^{6'}$ represents a (C_1-C_6 alkoxy)carbonyl group, the alkyl moiety thereof may be any one of those alkyl groups as defined for R^1 and R^2, but is preferably a methyl or ethyl group, and the alkoxycarbonyl group represented by R^3, R^6 or $R^{6'}$ is therefore preferably a methoxycarbonyl or ethoxycarbonyl group. Where R^3, R^6 or $R^{6'}$ represents an aralkyloxycarbonyl group, the aralkyl moiety thereof may be any one of those included within the araliphatic acyl group represented by R^3, R^6 or $R^{6'}$, but is preferably a benzoyloxycarbonyl group.

Where R^4 and R^5 represent alkyl groups, they may be the same or different and may be straight or branched chain alkyl groups. They preferably have from 1 to 5 carbon atoms and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and isopentyl groups.

Where R^4 and R^5 represent alkoxy groups, these

may be the same or different and may be straight or branched chain groups, preferably having from 1 to 4 carbon atoms. Examples include the methoxy, ethoxy, propoxy, isopropoxy and butoxy groups. Alternatively, R^4 and R^5 may together represent a C_1-C_4 alkylenedioxy group, more preferably a methylenedioxy or ethylenedioxy group.

Preferred classes of compounds of the present invention are as follows:

(1) Compounds in which R^3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an aromatic acyl group or a heterocyclic acyl group.

(2) Compounds in which Y represents an oxygen atom; R^1 and R^2 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; R^3 represents a hydrogen atom, a C_1-C_6 aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group; and R^4 and R^5 are the same or different and each represents a hydrogen atom, a C_1-C_5 alkyl group or a C_1 or C_2 alkoxy group.

(3) Compounds as defined in (2) above, in which: R^1, R^2, R^4 and R^5 are the same or different and each represents a hydrogen atom or a C_1-C_5 alkyl group; n is 1 or 2; and W represents the $-CH_2-$ or >CO group.

(4) Compounds as defined in (3) above, in which R^3 represents a hydrogen atom, a C_1-C_5 aliphatic acyl group, a benzoyl group or a nicotinoyl group.

(5) Compounds as defined in (4) above, in which: R^1 and R^4 are the same or different and each represents a C_1-C_5 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents a hydrogen atom or a C_1-C_4 aliphatic acyl group.

(6) Compounds in which: W represents the $-CH_2-$ or >CO group; Y and Z both represent oxygen atoms; n is 1 or 2; R^1 and R^4 are the same or different and each represents a C_1-C_4 alkyl group; R^2 and R^5 are the same or different and each represents the hydrogen atom or the methyl group; and R^3 represents a hydrogen atom or a C_1-C_4 aliphatic acyl group.

(7) Compounds as defined in (6) above, in which n is 1.

(8) Compounds as defined in (6) or (7) above, in which W represents the $-CH_2-$ group.

Preferred compounds among the compounds of this invention are those wherein: R^1 is a C_1-C_4 alkyl group, more preferably a methyl or isobutyl group, most

preferably a methyl group; R^2 is a hydrogen atom or a C_1-C_4 alkyl group, preferably a hydrogen atom, or a methyl or isopropyl group, more preferably a hydrogen atom or a methyl group, most preferably a methyl group; R^3 is a hydrogen atom, a C_1-C_4 aliphatic acyl group, an aromatic acyl group or a pyridinecarbonyl group, preferably a hydrogen atom, or an acetyl, butyryl, benzoyl or nicotinoyl group, more preferably a hydrogen atom or an acetyl, butyryl or benzoyl group, most preferably a hydrogen atom or an acetyl group; R^4 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a methyl, isopropyl, t-butyl or methoxy group, more preferably a methyl or t-butyl group, most preferably a methyl group; R^5 is a hydrogen atom, a C_1-C_4 alkyl group or a C_1 or C_2 alkoxy group, preferably a hydrogen atom, or a methyl or methoxy group, more preferably a hydrogen atom or a methyl group and most preferably a methyl group; n is 1 or 2, preferably 1; Y is an oxygen atom; Z is an oxygen atom or an imino group, most preferably an oxygen atom; and W is a $-CH_2-$ or $>C=O$ group, preferably a $-CH_2-$ group.

Specific examples of compounds of the present invention are given in the following list:

[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-
oxy)benzyl]thiazolidine-2,4-dione

2. 5-[4-(6-hydroxy-2,5,7-trimethylchroman-2-
ylmethoxy)benzyl]thiazolidine-2,4-dione

3. 5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-
ylmethoxy)benzyl]thiazolidine-2,4-dione

4. 5-[4-(6-hydroxy-2-methylchroman-2-ylmethoxy)-
benzyl]thiazolidine-2,4-dione

5. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-
ylmethoxy)benzyl]thiazolidine-2,4-dione

6. 5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-
ylmethoxy)benzyl]thiazolidine-2,4-dione

7. 5-[4-(6-hydroxy-2,7,8-trimethylchroman-2-
ylmethoxy)benzyl]thiazolidine-2,4-dione

8. 5-[4-(6-hydroxy-7-isopropyl-2-methylchroman-2-
ylmethoxy)benzyl]thiazolidine-2,4-dione

9. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methylchroman-2-
ylmethoxy)benzyl]thiazolidine-2,4-dione

10. 5-[4-(6-hydroxy-2-methyl-7-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

11. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

12. 5-{4-[2-(6-hydroxy-2,5,7-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

13. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

14. 5-{4-[2-(6-hydroxy-2-methylchroman-2-yl)ethoxy]-benzyl}thiazolidine-2,4-dione

15. 5-{4-[2-(2-ethyl-6-hydroxy-5,7,8-trimethyl-chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

16. 5-{4-[2-(6-hydroxy-5,7,8-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

17. 5-{4-[2-(6-hydroxy-5,7-diisopropyl-2,8-dimethyl-chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

18. 5-{4-[2-(6-hydroxy-7-pentyl-2-propylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

19. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

20. 5-[4-(6-hydroxy-7,8-dimethoxy-5-methyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

21. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

22. 5-[4-(6-hydroxy-2,5-dimethyl-7,8-methylenedioxy-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

23. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

24. 5-{4-[3-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione

25. 5-{4-[3-(7-t-butyl-6-hydroxychroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione

26. 5-[4-(6-hydroxychroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione

27. 5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione

28. 5-[4-(6-hydroxy-5,7,8-trimethyl-2-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

29. 5-[4-(7-t-butyl-6-hydroxy-2-isopropylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

30. 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

31. 5-[4-(6-hydroxy-2-isobutyl-7-isopropylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

32. 5-[4-(6-hydroxy-5,7,8-trimethyl-2-pentylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

33. 5-[4-(6-hydroxy-2-isopentyl-5,7-dimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

34. 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

35. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

36. 5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

37. 5-[4-(6-hydroxy-2-methylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

38. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

39. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-chroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

40. 5-[4-(6-hydroxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

41. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-chroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

42. 5-[4-(6-hydroxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

43. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

44. 5-{4-[2-(6-hydroxy-2-methylchroman-2-yl)ethoxy]-benzyl}-2-iminothiazolidin-4-one

45. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

46. 5-[4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl]-2-iminothiazolidin-4-one

47. 5-[4-[2-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methylchroman-2-yl)ethoxy]benzyl]-2-iminothiazolidin-4-one

48. 5-[4-[2-(6-hydroxy-7,8-dimethoxy-5-methylchroman-2-yl)ethoxy]benzyl]-2-iminothiazolidin-4-one

49. 5-[4-[3-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)propoxy]benzyl]-2-iminothiazolidin-4-one

50. 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

51. 5-[4-(6-hydroxy-2,5,7-trimethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

52. 5-[4-(7-t-butyl-6-hydroxy-2-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

53. 5-[4-(6-hydroxy-2-methylchroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine

54. 5-[4-(7-t-butyl-6-hydroxychroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine

55. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-chroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

56. 5-[4-(6-hydroxy-7,8-dimethoxy-5-methyl-chroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

57. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-chroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

58. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine

59. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine

60. 5-{4-[2-(6-hydroxy-2-methylchroman-2-yl)ethoxy]-benzyl}-2,4-diiminothiazolidine

61. 5-{4-[3-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-chroman-2-yl)propoxy]benzyl}-2,4-diiminothiazolidine

62. 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

63. 5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

64. 5-[4-(6-acetoxy-7-t-butyl-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

65. 5-[4-(6-acetoxy-2-methylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione

66. 5-[4-(2-ethyl-6-isobutyryloxy-5,7,8-trimethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

67. 5-[4-(6-butyryloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

68. 5-{4-[2-(6-m-fluorobenzoyloxy-2,5,7-trimethyl-chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

69. 5-{4-[2-(6-acryloyloxy-7-t-butyl-2-methyl-chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

70. 5-{4-[2-(6-heptanoyloxy-2-methylchroman-2-yl)-ethoxy]benzyl}thiazolidine-2,4-dione

71. 5-{4-[2-(6-p-aminobenzoyloxy-2-ethyl-5,7,8-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

72. 5-{4-[2-(5,7,8-trimethyl-6-3'-thenoyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

73. 5-{4-[2-(6-2'-furoyloxy-5,7-diisopropyl-2,8-dimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

74. 5-{4-[2-(6-β-naphthoyloxy-7-pentyl-2-propyl-chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

75. 5-[4-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

76. 5-{4-[6-(3,5-dichlorobenzoyloxy)-7,8-dimethoxy-5-methylchroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione

77. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-6-valeryloxy-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

78. 5-[4-(6-isonicotinoyloxy-2,5-dimethyl-7,8-methyl-enedioxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

79. 5-{4-[2-(7,8-dimethoxy-2,5-dimethyl-6-p-nitro-benzoyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

80. 5-{4-[3-(6-o-chlorobenzoyloxy-2,5,7,8-tetramethylchroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione

81. 5-{4-[3-(7-t-butyl-6-m-dimethylaminobenzoyloxy-5-methylchroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione

82. 5-[4-(6-acetoxychroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione

83. 5-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

84. 5-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

85. 5-[4-(6-acetoxy-5,7-diisopropyl-2-methylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

86. 5-{4-[7-t-butyl-6-(3,5-di-t-butyl-4-hydroxybenzoyloxy)-2-methylchroman-2-ylmethoxy]benzyl}-2-iminothiazolidin-4-one

87. 5-[4-(6-acetoxy-2-methylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

88. 5-[4-(2-ethyl-5,7,8-trimethyl-6-phenylacetoxy-chroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

89. 5-[4-(6-cinnamoyloxy-7,8-dimethoxy-2,5-dimethyl-chroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

90. 5-[4-(6-m-chlorobenzoyloxy-7,8-dimethoxy-5-methyl-chroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

91. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-6-valeryloxy-chroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

92. 5-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2-iminothiazolidin-4-one

93. 5-{4-[2-(6-o-methoxybenzoyloxy-2,5,7,8-tetra-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

94. 5-{4-[2-(2-methyl-6-pivaloyloxychroman-2-yl)-ethoxy]benzyl}-2-iminothiazolidin-4-one

95. 5-{4-[2-(7-t-butyl-2-methyl-6-propionyloxy-chroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

96. 5-{4-[2-(6-ethoxycarbonyloxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-

4-one

97. 5-{4-[2-(6-p-chlorophenylacetoxy-2-ethyl-7,8-dimethoxy-5-methylchroman-2-yl)ethoxy]benzyl}-2-imino-thiazolidin-4-one

98. 5-{4-[2-(7,8-dimethoxy-5-methyl-6-3'-phenylpropionyloxychroman-2-yl)ethoxy]benzyl}-2-imino-thiazolidin-4-one

99. 5-{4-[3-(6-benzyloxycarbonyloxy-2,5,7,8-tetra-methylchroman-2-yl)propoxy]benzyl}-2-iminothiazolidin-4-one

100. 5-[4-(6-benzoyloxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

101. 5-[4-(6-cyclohexanecarbonyloxy-2,5,7-tri-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

102. 5-[4-(6-acetoxy-7-t-butyl-2-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

103. 5-[4-(6-acetoxy-2-methylchroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine

104. 5-[4-(6-acetoxy-7-t-butylchroman-2-ylmethoxy)-

benzyl]-2,4-diiminothiazolidine

115. 5-[4-(6-acetoxy-2,7-dimethylchroman-2-ylmethoxy)-benzyl]-2,4-diiminothiazolidine

116. 5-[4-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

117. 5-[4-(6-acetoxy-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

118. 5-[4-(6-acetoxy-2-ethyl-7,8-dimethoxy-5-methylchroman-2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

119. 5-{4-[2-(6-methoxycarbonyloxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine

120. 5-{4-[2-(7-t-butyl-6-cyclopentanecarbonyloxy-2-methylchroman-2-yl)ethoxy]benzyl}-2,4-diiminothiazolidine

121. 5-{4-[2-(6-formyloxy-2-methylchroman-2-yl)-ethoxy]benzyl}-2,4-diiminothiazolidine

122. 5-{4-[3-(6-methacryloyloxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)propoxy]benzyl}-2,4-

diiminothiazolidine

113. 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

114. 5-[4-(4,6-dihydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

115. 5-[4-(6-hydroxy-2,5,7-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

116. 5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

117. 5-[4-(7-t-butyl-4,6-dihydroxy-2-methylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

118. 5-[4-(6-hydroxy-2-methyl-4-oxochroman-2-yl-methoxy)benzyl]thiazolidine-2,4-dione

119. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

120. 5-[4-(2-ethyl-4,6-dihydroxy-5,7,8-trimethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

121. 5-[4-(6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-

ylmethoxy)benzyl]thiazolidine-2,4-dione

122. 5-[4-(6-hydroxy-2,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

123. 5-[4-(6-hydroxy-7-isopropyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

124. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

125. 5-[4-(6-hydroxy-2-methyl-4-oxo-7-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

126. 5-[4-[2-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione

127. 5-[4-[2-(4,6-dihydroxy-2,5,7,8-tetramethylchroman-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione

128. 5-[4-[2-(6-hydroxy-2,5,7-trimethyl-4-oxochroman-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione

129. 5-[4-[2-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-yl)ethoxy]benzyl]thiazolidine-2,4-dione

130. 5-[4-[2-(7-t-butyl-4,6-dihydroxy-2-methyl-

chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

131. 5-{4-[2-(6-hydroxy-2-methyl-4-oxochroman-2-yl)-ethoxy]benzyl}thiazolidine-2,4-dione

132. 5-{4-[2-(2-ethyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

133. 5-{4-[2-(6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

134. 5-{4-[2-(6-hydroxy-5,7-diisopropyl-2,8-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

135. 5-{4-[2-(6-hydroxy-4-oxo-7-pentyl-2-propyl-chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

136. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxo-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

137. 5-[4-(6-hydroxy-7,8-dimethoxy-5-methyl-4-oxo-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

138. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

139. 5-[4-(6-hydroxy-2,5-dimethyl-7,8-methylenedioxy-

4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

140. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

141. 5-{4-[3-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione

142. 5-{4-[3-(7-t-butyl-6-hydroxy-4-oxochroman-2-yl)propoxy]benzyl}thiazolidine-2,4-dione

143. 5-[4-(6-hydroxy-4-oxochroman-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione

144. 5-[4-(6-hydroxy-2,7-dimethyl-4-oxochroman-2-yl-methoxy)benzyl]thiazolidine-2,4-dione

145. 5-[4-(6-hydroxy-5,7,8-trimethyl-4-oxo-2-propylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

146. 5-[4-(7-t-butyl-6-hydroxy-2-isopropyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

147. 5-[4-(2-butyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

148. 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-

oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

149. 5-[4-(4,6-dihydroxy-2-isobutyl-5,7,8-trimethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

150. 5-[4-(2-t-butyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

151. 5-[4-(6-hydroxy-2-isobutyl-7-isopropyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

152. 5-[4-(6-hydroxy-5,7-dimethyl-4-oxo-2-pentyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

153. 5-[4-(6-hydroxy-5,7,8-trimethyl-2-pentyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

154. 5-[4-(6-hydroxy-2-isopentyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

155. 5-{4-[6-hydroxy-5,7,8-trimethyl-2-(2-methyl-butyl)-4-oxochroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione

156. 5-{4-[2-(2,2-dimethylpropyl)-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione

157. 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

158. 5-[4-(6-hydroxy-5,7-diisopropyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

159. 5-[4-(7-t-butyl-6-hydroxy-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

160. 5-[4-(6-hydroxy-2-methyl-4-oxochroman-2-yl-methoxy)benzyl]-2-iminothiazolidin-4-one

161. 5-[4-(2-ethyl-6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

162. 5-[4-(6-hydroxy-2-isobutyl-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

163. 5-[4-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxo-chroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

164. 5-[4-(6-hydroxy-5,7,8-trimethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

165. 5-[4-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

166. 5-[4-(6-hydroxy-2,7-dimethyl-4-oxochroman-2-yl-methoxy)benzyl]-2-iminothiazolidin-4-one

167. 5-{4-[2-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

168. 5-{4-[2-(6-hydroxy-2-methyl-4-oxochroman-2-yl)-ethoxy]benzyl}-2-iminothiazolidin-4-one

169. 5-{4-[2-(7-t-butyl-6-hydroxy-2-methyl-4-oxo-chroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

170. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

171. 5-{4-[2-(2-ethyl-6-hydroxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-imino-thiazolidin-4-one

172. 5-{4-[2-(6-hydroxy-7,8-dimethoxy-5-methyl-4-oxo-chroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

173. 5-{4-[3-(6-hydroxy-2,5,7,8-tetramethyl-4-oxo-chroman-2-yl)propoxy]benzyl}-2-iminothiazolidin-4-one

174. 5-[4-(6-hydroxy-2,5,7,8-tetramethyl-4-oxochroman-

2-ylmethoxy)benzyl]-2,4-diiminothiazolidine

175. 5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxo-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

176. 5-[4-(6-acetoxy-4-hydroxy-2,5,7,8-tetramethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

177. 5-[4-(4,6-diacetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

178. 5-[4-(6-acetoxy-4-benzoyloxy-2,5,7,8-tetramethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

179. 5-[4-(4-acetoxy-6-benzoyloxy-2,5,7,8-tetramethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

180. 5-[4-(4,6-dibenzoyloxy-2,5,7,8-tetramethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

181. 5-[4-(2-ethyl-4,6-diisobutyryloxy-5,7,8-trimethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

182. 5-[4-(4,6-dibutyryloxy-2,5,7,8-tetramethyl-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

183. 5-[4-[2-(6-m-fluorobenzoyloxy-4-heptanoyloxy-

2,5,7-trimethylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

184. 5-{4-[2-(4,6-diacryloyloxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

185. 5-{4-[2-(4-m-fluorobenzoyloxy-6-heptanoyloxy-2-methylchroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

186. 5-{4-[2-(5,7,8-trimethyl-4,6-bis{3-thenoyloxy}chroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

187. 5-{4-[2-(4,6-bis{2-furoyloxy}-5,7-di-isopropyl-2,8-dimethylchroman-2-yl)ethoxy]benzyl}-thiazolidine-2,4-dione

188. 5-[4-(2,5,7,8-tetramethyl-4,6-dinicotinoyloxy-chroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

189. 5-{4-[4,6-bis(3,5-dichlorobenzoyloxy)-7,8-dimethoxy-5-methylchroman-2-ylmethoxy]benzyl}-thiazolidine-2,4-dione

190. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-4,6-divaleryloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

191. 5-{4-[7-t-butyl-6-(3,5-di-t-butyl-4-hydroxybenzoyloxy)-2-methyl-4-oxochroman-2-ylmethoxy]benzyl}thiazolidine-2,4-dione

192. 5-[4-(2-ethyl-5,7,8-trimethyl-4-oxo-6-phenylacetoxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

193. 5-[4-(6-cinnamoyloxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

194. 5-[4-(6-m-chlorobenzoyloxy-7,8-dimethoxy-5-methyl-4-oxochroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

195. 5-[4-(2-ethyl-7,8-dimethoxy-5-methyl-4-oxo-6-valeryloxychroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione

196. 5-{4-[2-(6-o-methoxybenzoyloxy-2,5,7,8-tetramethyl-4-oxochroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

197. 5-{4-[2-(2-methyl-4-oxo-6-pivaloyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

198. 5-{4-[2-(7-t-butyl-2-methyl-4-oxo-6-propionyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

199. 5-{4-[2-(6-ethoxycarbonyloxy-7,8-dimethoxy-2,5-dimethyl-4-oxochroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

200. 5-{4-[2-(6-p-chlorophenylacetoxy-2-ethyl-7,8-dimethoxy-5-methyl-4-oxochroman-2-yl)ethoxy]benzyl}-thiazolidine-2,4-dione

201. 5-[4-{2-[7,8-dimethoxy-5-methyl-4-oxo-6-(3-phenylpropionyloxy)chroman-2-yl]ethoxy}benzyl]-thiazolidine-2,4-dione

202. 5-[4-(6-cyclohexanecarbonyloxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2,4-diimino-thiazolidine

203. 5-[4-(6-acetoxy-2,5,7,8-tetramethyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

204. 5-[4-(6-acetoxy-7-t-butyl-2-methyl-4-oxochroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

205. 5-[4-(6-acetoxy-5,7,8-trimethylchroman-2-ylmethoxy)benzyl]-2-iminothiazolidin-4-one

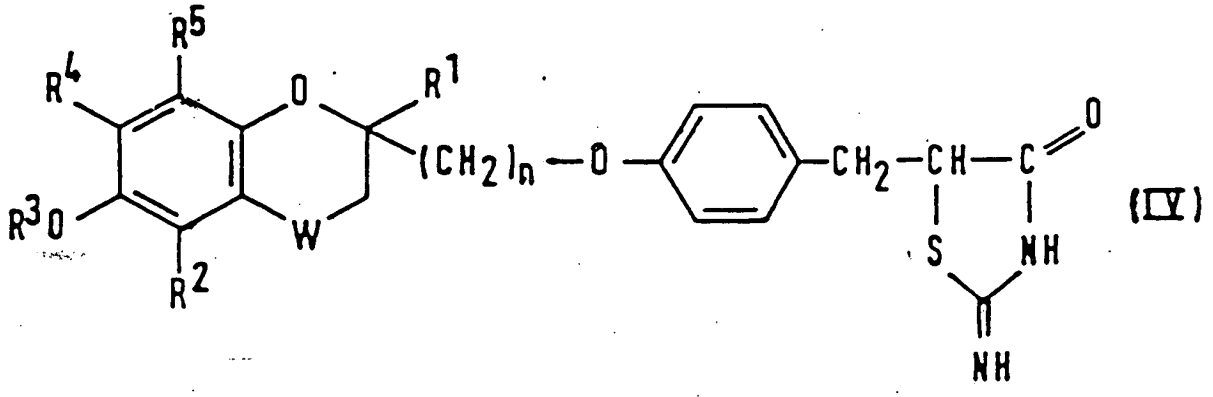
206. 5-{4-[2-(6-acetoxy-7-t-butyl-2-methylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

207. 5-{4-[2-(6-acetoxy-7,8-dimethoxy-2,5-dimethylchroman-2-yl)ethoxy]benzyl}-2-iminothiazolidin-4-one

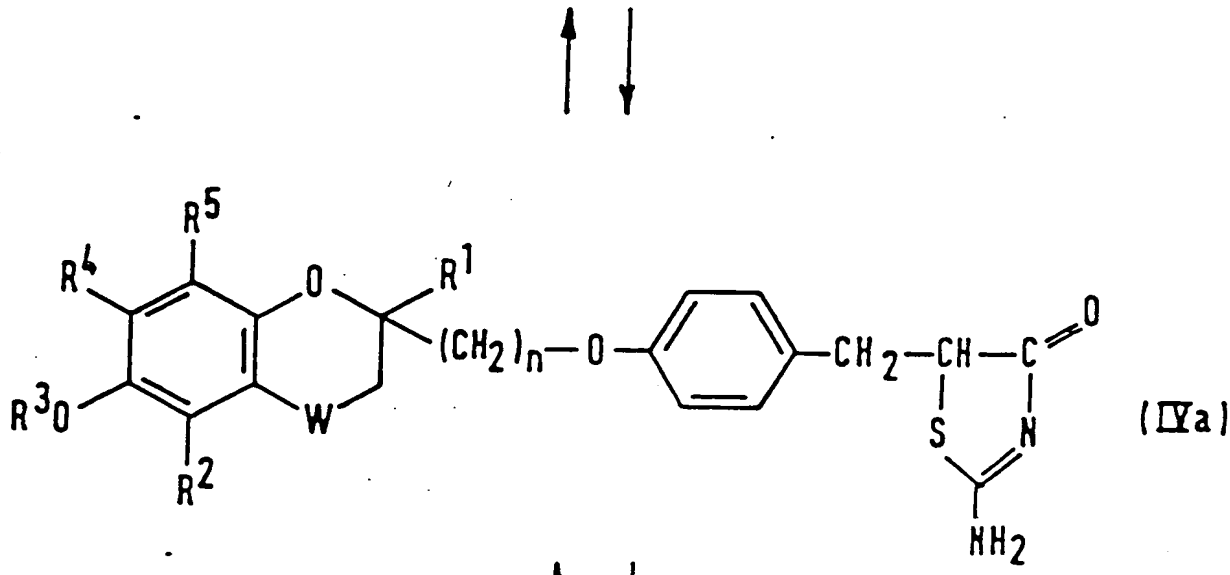
208. 5-{4-[2-(2,5,7,8-tetramethyl-6-nicotinoyloxychroman-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione

Of the compounds listed above, preferred compounds are Compounds No. 1, 5, 6, 11, 13, 23, 27, 30, 34, 36, 38, 40, 42, 62, 63, 67, 75, 113, 116, 148, 157, 159, 162, 175, 205, 206, and 207. More preferred compounds are Compounds No. 1, 5, 13, 30, 62, 67, 113 and 116 and the most preferred compounds are Compounds No. 1 and 62.

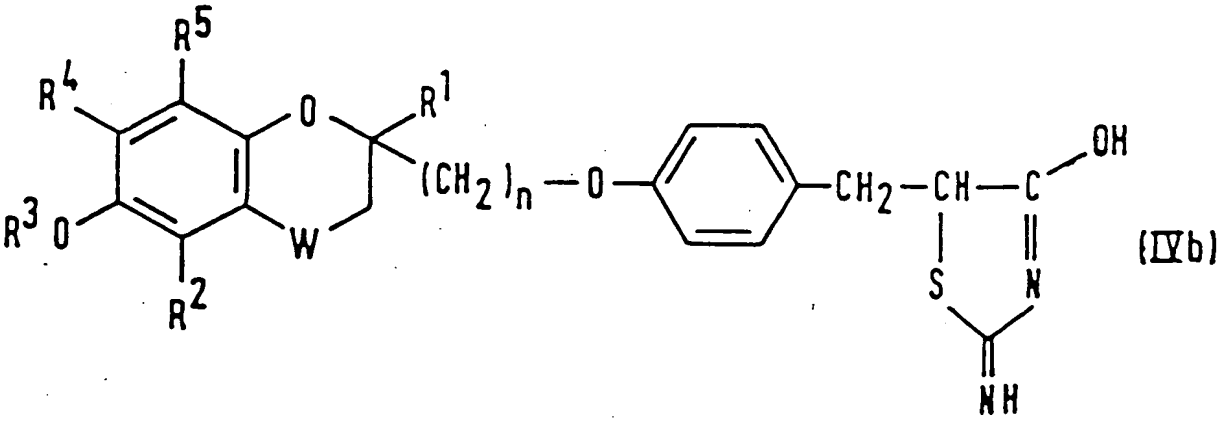
Various of the compounds of the invention can exist in the form of tautomers. For example, those compounds of the invention in which Z represents an imino group and Y represents an oxygen atom can exist in the form of the tautomers (IV), (IVa) and (IVb):



(IV)



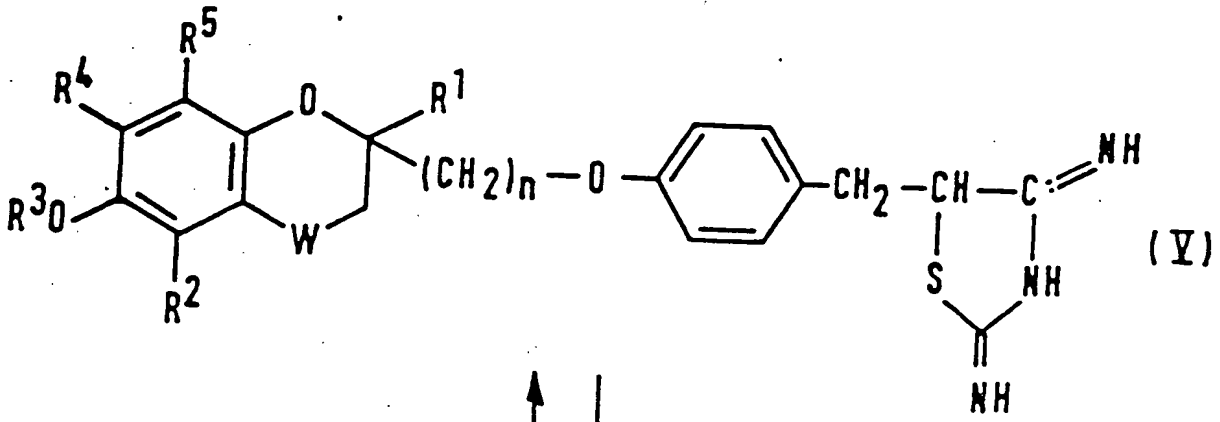
(IVa)



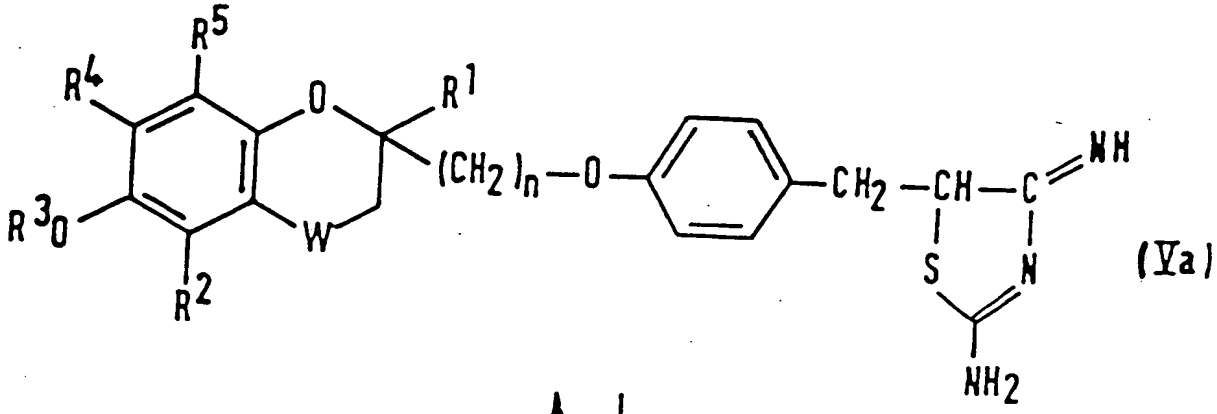
(IVb)

Compounds in which both Y and Z represent imino groups can exist in the form of the tautomers (V), (Va)

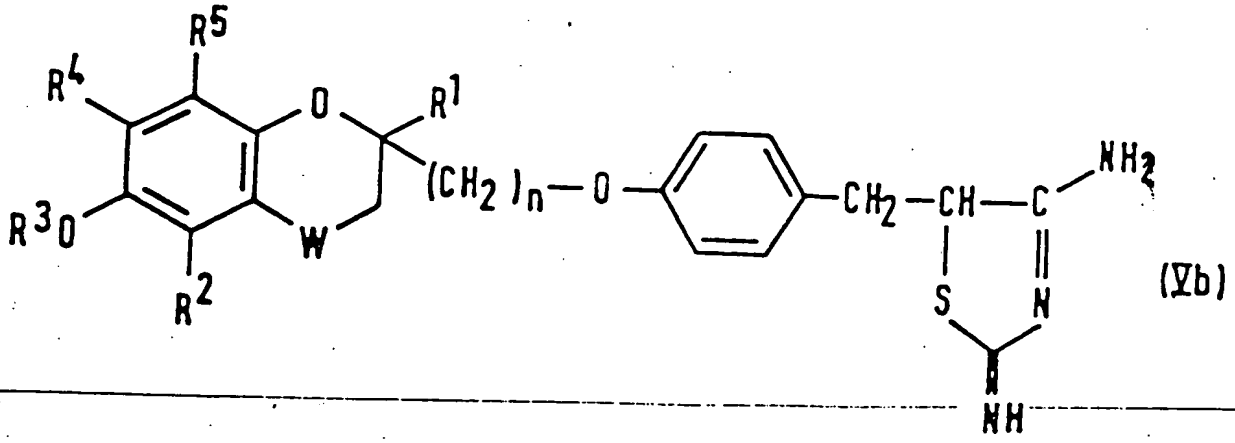
and (Vb):



(V)

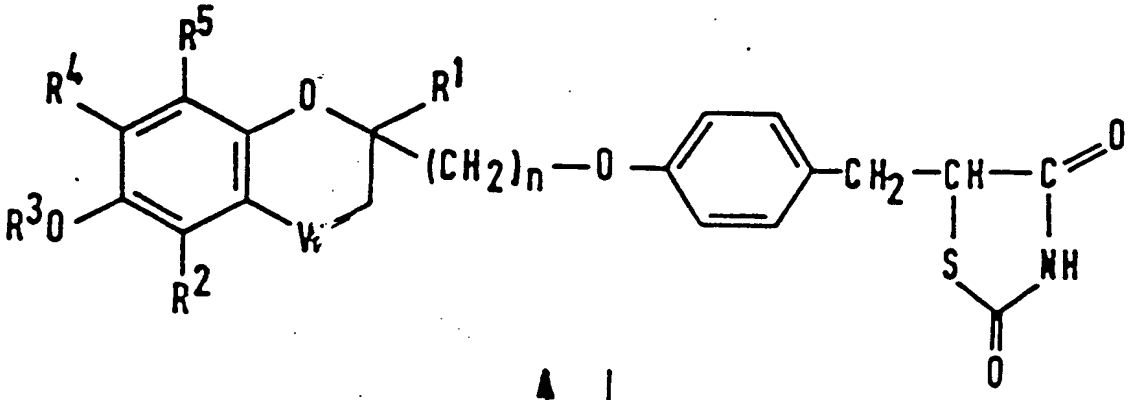


(Va)

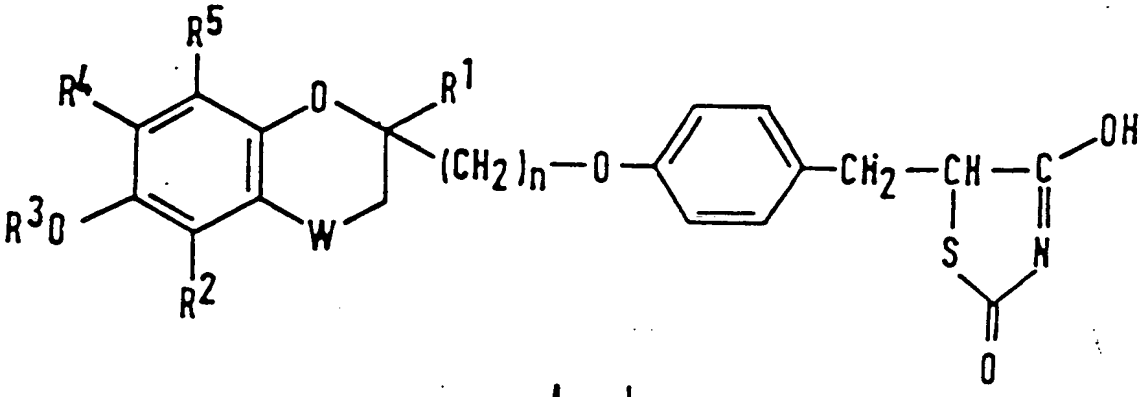


(Vb)

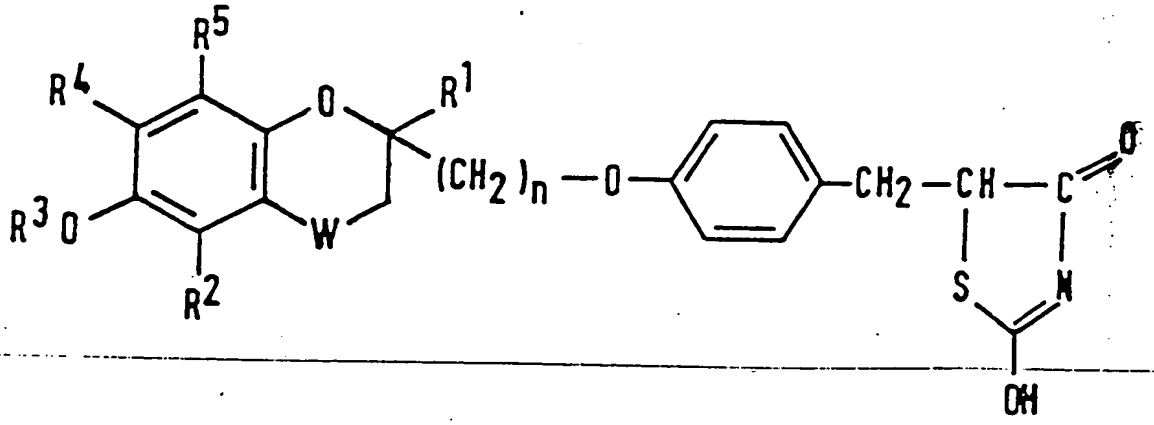
Compounds in which Y and Z both represent oxygen atoms can exist in the form of the tautomers (VI), (VIa) and (VIb):



(VI)



(VIa)



(VIb)

For convenience, all of the tautomers are represented by a single formula, but the tautomeric nature of these compounds should be remembered, as it can have an effect upon various of the properties of the compounds, including their salt-forming ability, as discussed hereafter.

In addition, the compounds of the invention can exist in the form of various stereoisomers. For example, where W represents a >C=O or $-CH_2-$ group, the carbon atoms at the 2- position of the chroman ring and the 5- position of the thiazolidine ring are both asymmetric. Furthermore, where W represents a $>CH-OR^6$ group, the carbon atoms at the 2- and 4- positions of the chroman ring and at the 5- position of the thiazolidine ring are asymmetric. All of these thus give rise to the possibility of stereoisomers. All of the isomers are represented herein by a single formula, and the present invention envisages both mixtures of the isomers and the individual isomers, which may be separated from each other by conventional means.

The compounds of the present invention also include salts of compounds of the invention described above, which may be salts with cations. Cations with which the compounds of the invention may form salts include: alkali metals, such as sodium or potassium; alkaline

earth metals, such as calcium; and trivalent metals, such as aluminium.

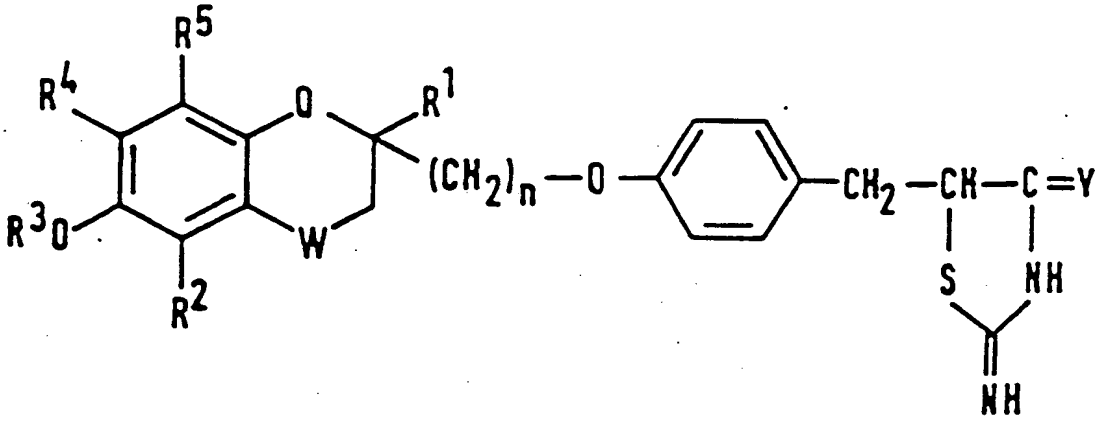
It will, however, be appreciated that the particular nature of the salt employed is not critical to the present invention and any cations known in the art for forming salts of this type may equally be used in the present invention. The only constraint is that the cations should not, or should not to an unacceptable extent, increase the toxicity or reduce the activity of the resulting compound.

Because the compounds of the invention contain a number of salt-forming centres, mono- and di- salts may be formed. For example, because of the tautomerism described above in relation to the compounds of formula (VI), there are two potential salt-forming reactive sites at the oxygen atom in the group $-OR^3$ and the nitrogen atom at the 3- position of the thiazolidine ring.

PREPARATION OF NEW COMPOUNDS

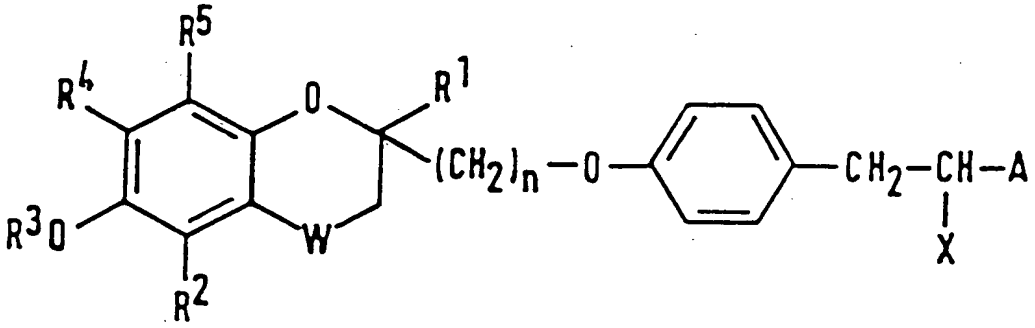
Step (a)

Compounds of the invention in which Z represents an imino group, that is to say compounds of formula (III):



(III)

(in which R^1-R^5, n, W and Y are as defined above) may be prepared by reacting a compound of formula (II):



(II)

[in which R^1-R^5 and n are as defined above, A represents a cyano group, a carboxy group, an alkoxycarbonyl group, a carbamoyl group or a group of formula $-COO(M)_m$, in which M represents a cation and m is the reciprocal of its valency, and X represents a

halogen atom) with thiourea.

Where A represents a cyano group, the product is a compound in which Y represents an imino group; where A represents a carboxy, alkoxycarbonyl, carbamoyl or $-COO(M)_m$ group, the product is a compound where Y represents an oxygen atom.

In the above formula (II), where A represents an alkoxycarbonyl group, this is preferably a (C_1-C_6 alkoxy)carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl or butoxycarbonyl group. M preferably represents a metal atom, such as a sodium, potassium, calcium or aluminium atom, or an ammonium group. X preferably represents a chlorine, bromine or iodine atom.

This reaction is preferably applied only to those compounds where W represents a $-CH_2-$ or >C=O group, compounds in which W represents a $>CH-OR^6$ group being prepared from the corresponding compound where W represents a >C=O group, as explained hereafter.

Reaction of the compound of formula (II) with thiourea is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect on the reaction. Suitable

solvents include: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; ethers, such as tetrahydrofuran or dioxane; ketones, such as acetone; dimethyl sulphoxide; sulpholane; or amides, such as dimethylformamide.

There is no particular limitation on the molar ratio of the compound of formula (II) to thiourea; however, we would normally prefer to use equimolar amounts or a molar excess of thiourea, preferably a slight molar excess. In general, from 1 to 2 moles of thiourea per mole of the compound of formula (II) are preferred.

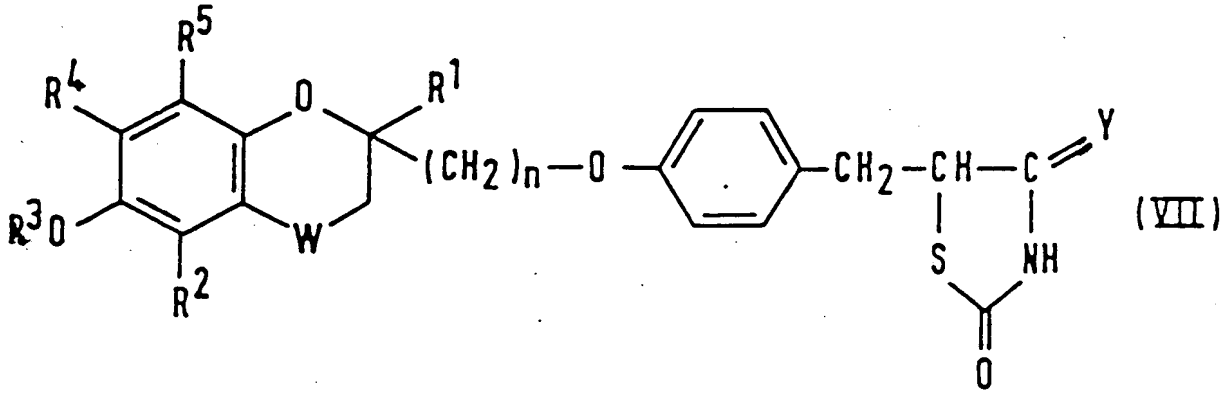
The various reaction conditions, such as the reaction temperature and time, will vary, depending upon the natures of the starting materials and the solvent; however, the reaction is normally effected at the reflux temperature of the solvent or at a temperature of from 80 to 150°C for a period of from 1 to 20 hours.

The resulting compound of formula (III) may be the desired final product of the present invention, in which case it may be isolated from the reaction mixture by conventional means, as discussed hereafter. Alternatively, with or without isolation and/or purification, the compound of formula (III) may be subjected to one or both of steps (b) and (c), in any

order, and, if desired, step (c) may be followed by step (d). The product of any of these steps may be subjected to the salification reaction discussed in step (e).

Step (b)

In this step, the compound of formula (III), that is to say a compound of formula (I) in which Z represents an imino group, may be hydrolysed to give the corresponding compound of formula (I) in which Z represents an oxygen atom, that is to say a compound of formula (VII):



(VII)

(in which R^1-R^5, n, W and Y are as defined above).

The hydrolysis reaction is preferably carried out by heating the compound of formula (III) in a suitable solvent with water and an organic acid (such as acetic

acid) or a mineral acid (such as sulphuric acid or hydrochloric acid). The nature of the solvent is not critical to the invention, provided that it has no adverse effect upon the reaction; suitable solvents include: sulpholane; and alcohols, such as methanol, ethanol or ethylene glycol monomethyl ether.

The amount of acid used is preferably from 0.1 to 10 moles, more preferably from 0.2 to 3 moles, per mole of the compound of formula (III). The water or aqueous solvent is preferably employed in a large molar excess over the compound of formula (III).

Although not critical, the temperature employed for the reaction is preferably from 50 to 100°C and the time required for the reaction is normally from 2 to 20 hours.

Where Y in the compound of formula (III) represents an imino group, the hydrolysis of the present step will normally likewise convert said imino group to an oxygen atom, the product being a compound in which both Y and Z are oxygen atoms. However, by careful control of the hydrolysis conditions, it is possible to prevent the hydrolysis reaction going to completion, in which case part of the product will be a compound in which Y represents an imino group and Z represents an oxygen atom.

In addition to converting the imino group represented by Z to an oxygen atom, where R^3 in the compound of formula (III) represents an acyl group, the hydrolysis reaction may convert this to a hydrogen atom, although it is possible to maintain the acyl group represented by R^3 intact, provided that appropriate reaction conditions are chosen, as is well-known in the art.

Where the compound of formula (VII) is a compound in which R^3 represents a hydrogen atom, this may be acylated to give a corresponding compound in which R^3 represents one of the acyl groups defined above. This acylation reaction may be carried out at any suitable stage in the reaction sequence and may, if desired, be carried out simultaneously with the acylation reaction of step (d), as described hereafter. Where, however, the acylation reaction is carried out separately from step (d), the conditions are preferably as follows:

The acylating agent is preferably an acid halide or an acid anhydride, or it may be an organic acid, such as an aromatic carboxylic acid or an aliphatic carboxylic acid, in association with a dehydrating agent or dehydrating catalyst such as a mineral acid (e.g. hydrochloric acid or sulphuric acid) or an organic acid (e.g. p-toluenesulphonic acid).

The reaction is normally carried out in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene or toluene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, such as methylene chloride or chloroform; ketones, such as acetone or methyl ethyl ketone; amides, such as dimethylformamide or dimethylacetamide; organic bases, such as pyridine or triethylamine; sulphoxides, such as dimethyl sulphoxide; sulphones, such as sulpholane; or water; a single one of these solvents or a mixture of any two or more thereof may be employed.

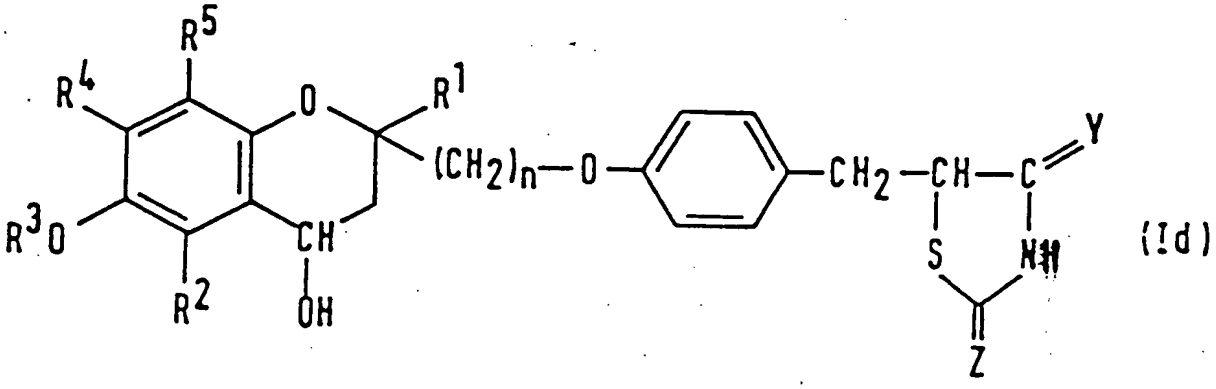
The ratio of the amount of the compound of formula (VII) in which R^3 represents a hydrogen atom to the amount of acylating agent is not particularly critical, but the use of a slight molar excess of the acylating agent over the compound of formula (VII) may be desirable. In general, we prefer to employ from 1 to 2 moles of acylating agent per mole of compound of formula (VII).

The reaction conditions, such as the reaction temperature and reaction time, will vary, depending upon

a number of factors, including the nature of the starting materials and solvent, but the reaction is generally carried out at a temperature of from 0 to 100°C for a period of from several minutes to about 20 hours.

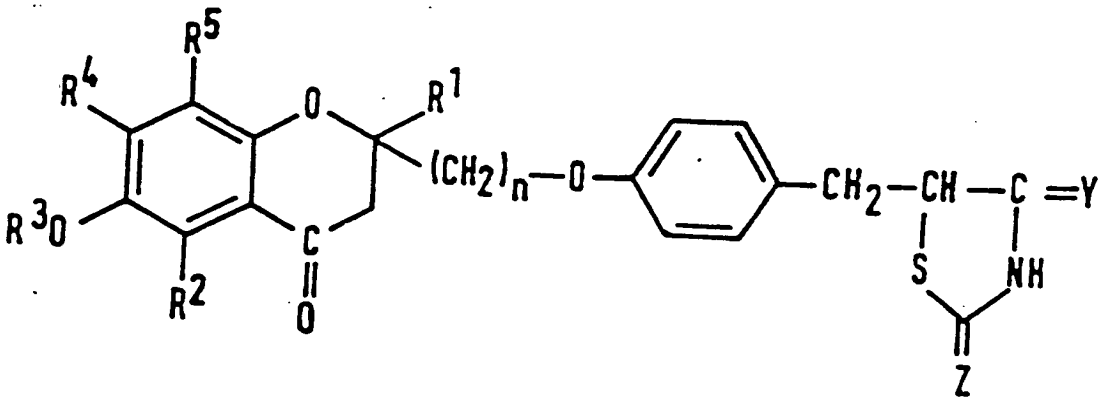
Step (c)

Compounds of formula (I) in which W represents a group of formula >CH-OH, that is to say compounds of formula (Id):



(Id)

(in which R^1-R^5, n, Y and Z are as defined above) may be prepared by reducing the corresponding compound in which W represents a group of formula >C=O, that is to say a compound of formula (Ib):



(Ib)

(in which R^1-R^5, n, Y and Z are as defined above).

The reducing agent employed for this reaction is any one which is capable of reducing a ring carbonyl group to a >CH-OH group without affecting, or affecting to a substantial degree, the remainder of the molecule. Suitable reducing agents include borohydrides, such as sodium borohydride, or K-Selectride, especially sodium borohydride.

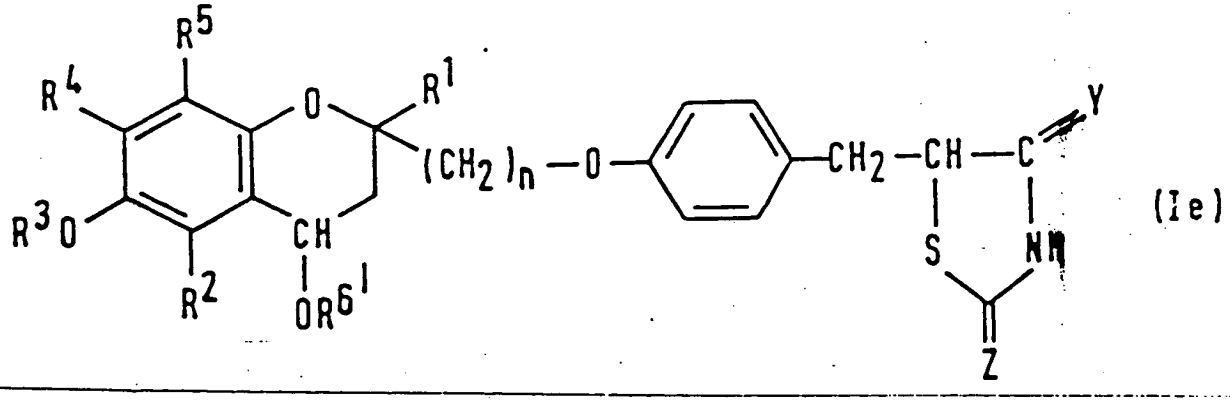
The reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include, for example: alcohols, such as methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether; and ethers, such as tetrahydrofuran or dioxane.

The molar ratio of the compound of formula (Ib) to the reducing agent is not critical, however we prefer to employ a molar excess of reducing agent, preferably from 1 to 20 moles of reducing agent (especially sodium borohydride) per mole of compound of formula (Ib).

The reaction conditions, particularly the reaction temperature and time, will vary depending upon a number of factors, especially the natures of the starting material, solvent and reducing agent. However, the reaction is normally carried out at a temperature of from 0 to 100°C for a period of from 1 to about 20 hours.

Step (d)

Optionally, compounds of formula (I) in which W represents a group of formula >CH-OR$^{6'}$ (in which R$^{6'}$ represents any one of the groups defined for R^6 but not the hydrogen atom), that is to say compounds of formula (Ie):



(Ie)

(in which R^1-R^5, $R^{6'}$, n, Y and Z are as defined above) may be prepared by acylating the corresponding compound of formula (Id), prepared as described in step (c).

The acylating agent is preferably an acid halide or acid anhydride, the parent acid of which will depend upon the acyl group $R^{6'}$ which it is desired should be introduced into the compound.

The acylation reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; aromatic hydrocarbons, such as benzene, toluene or xylene; aliphatic hydrocarbons, such as hexane, cyclohexane or heptane; halogenated hydrocarbons, such as methylene chloride or chloroform; organic bases, such as pyridine or triethylamine; amides, such as dimethylformamide or dimethylacetamide; sulphoxides, such as dimethyl sulphoxide; and sulphones, such as sulpholane.

The ratio of the amount of compound of formula (Id) to the acylating agent is not particularly critical and we therefore prefer to employ a slight molar excess of

acylating agent over compound (Id). In general, from 1 to 2 moles of acylating agent are employed per mole of compound of formula (Id).

The reaction conditions, particularly reaction temperature and time, will vary depending upon a number of factors, especially the natures of the starting material, acylating agent and solvent, but we normally prefer to carry out the reaction at a temperature of from 0 to 100°C for a period of from several minutes to about 20 hours.

Step (e)

The compounds of the invention, prepared as described in any of the above steps may be converted to their salts by conventional means, for example by reaction with a basic compound of an alkali metal (such as sodium or potassium), an alkaline earth metal (such as calcium) or a trivalent metal (such as aluminium). Preferred such compounds are sodium hydroxide, potassium hydroxide, sodium ethoxide and potassium t-butoxide.

It will be appreciated that the compounds produced in all of the above steps can exist in various tautomeric forms, as illustrated in relation to compounds (IV), (V) and (VI).

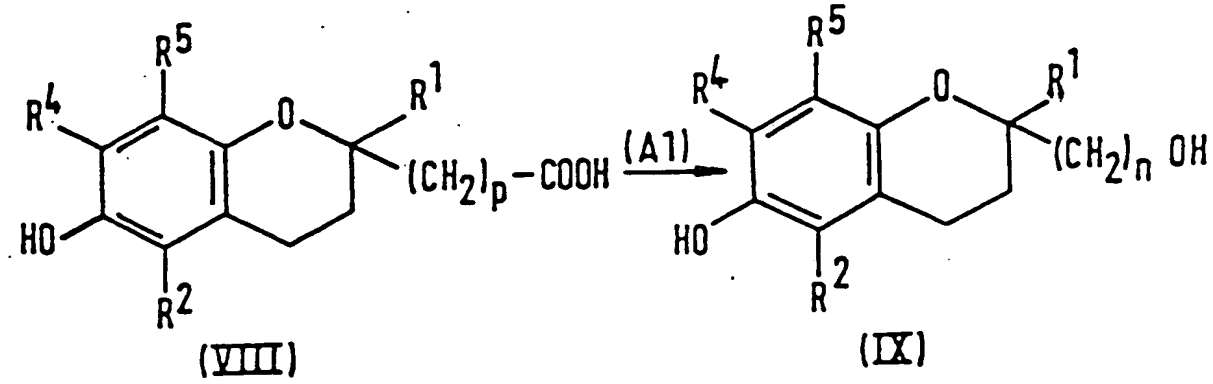
The compounds prepared as described in any of the above steps may be separated after that step and, if desired, purified by conventional means. Suitable isolation and purification steps include concentration of the reaction mixture by evaporating off the solvent under reduced pressure, extraction with a suitable solvent, recrystallization, transfer into another solvent, chromatography and optical resolution. However, where two or more of the above steps are to be carried out, they may, if desired, be carried out without intermediate isolation or purification.

PREPARATION OF STARTING MATERIALS

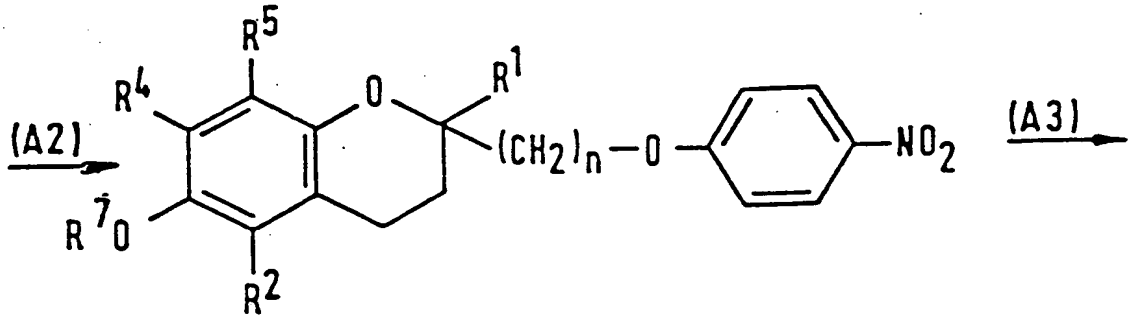
The α-halocarboxylic acid derivatives of formula (II), which are the principal starting materials for preparing the compounds of the invention, are novel compounds and may be prepared by Methods A and B described below.

Method A

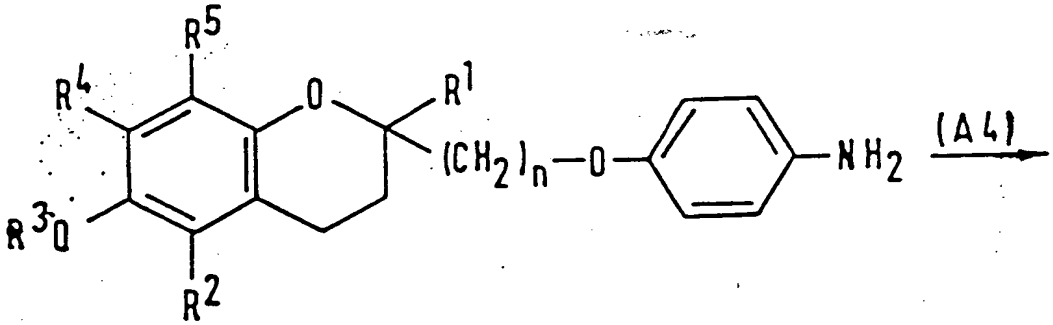
Compounds of formula (II) in which W represents a $-CH_2-$ group may be prepared by the sequence of reactions illustrated in the following reaction scheme:



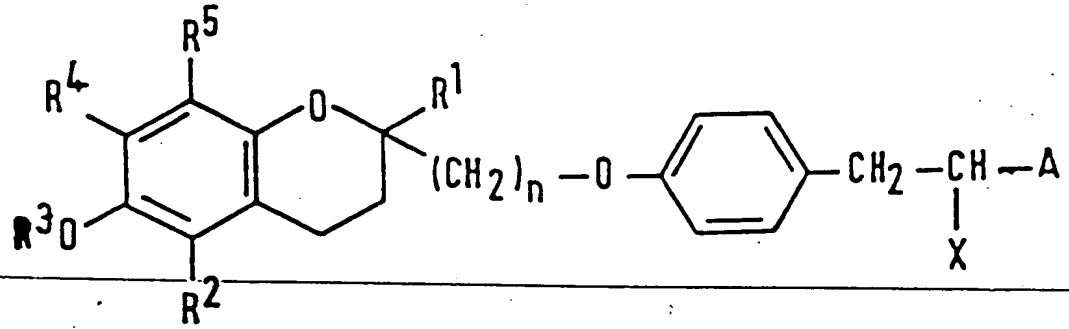
(VIII) (IX)



(X)



(XI)



(IIa)

In the above formulae, R^1-R^5, n, A and X are as defined above, p = (n-1); and R^7 represents a hydroxy-protecting group.

Step (A1)

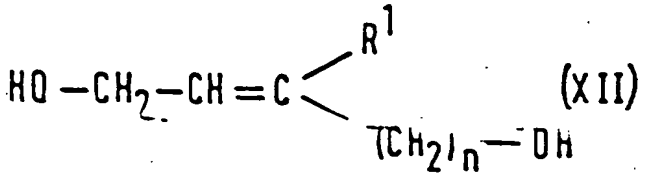
The chroman carboxylic acid homologues (VIII), which are the starting materials for this Method, may be prepared as described, for example, in the Journal of the American Oil Chemical Society, 51, 200 (1974).

These acids (VIII) are reduced with a reducing agent, such as lithium aluminium hydride or Vitride [sodium bis(2-methoxyethoxy)aluminium hydride], to give the corresponding chroman alcohol homologue (IX). This reaction is preferably effected in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reaction. Suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or ethylene glycol dimethyl ether; aromatic hydrocarbons, such as benzene, toluene or xylene; and aliphatic hydrocarbons, such as hexane, heptane, cyclohexane, petroleum ether, ligroin or ethylcyclohexane.

The ratio of the amount of acid (VIII) to reducing agent is not particularly critical, but we generally

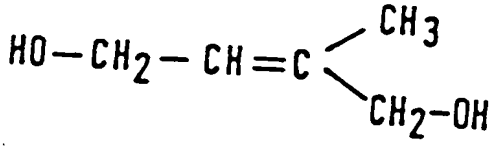
prefer to use a slight molar excess of reducing agent. Preferably the amount of reducing agent is from 1 to 2 moles per mole of acid (VIII). The reaction conditions, particularly the reaction temperature and time, will vary depending upon a number of factors, such as the nature of the starting material, the reducing agent and the solvent, but the reaction is generally carried out at a temperature of from 10 to 100°C for a period of from 10 minutes to 20 hours.

Alternatively, the chroman alcohol homologue (IX) may be prepared by reacting a hydroquinone with a compound of formula (XII):



(XII)

(in which n and R^1 are as defined above), e.g. a compound of formula (XIIa):



(XIIa)

in the presence of aluminium chloride, as described in West German Patent No. 3,010,504.

Step (A2)

The chroman alcohol homologues of formula (IX) obtained in step (A1) may be converted to the corresponding nitrophenoxyalkyl chroman compounds (X). However, before carrying out this reaction, we prefer that the phenolic hydroxy group should be protected by a hydroxy-protecting group R^7.

The nature of the hydroxy-protecting group is not critical and any such group commonly used in this type of reaction and compound may be employed. Suitable groups include: alkoxyalkyl groups, such as the methoxymethyl group; aralkyl groups, such as the benzyl group; the 2-tetrahydropyranyl group; and acyl groups,

such as the acetyl or benzoyl groups. The alkoxyalkyl groups are preferred. The reaction is normally effected by contacting a compound R^7X (in which R^7 is as defined above and X represents a halogen atom, preferably a chlorine atom), such as chloromethyl methyl ether or benzyl chloride, with the compound of formula (IX) in the presence of a base such as an alkali metal or alkaline earth metal hydride (e.g. sodium hydride or calcium hydride) or an alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide or potassium t-butoxide). The reaction is normally carried out in the presence of a solvent, for example: an ether, such as diethyl ether, tetrahydrofuran or dioxane; an aromatic hydrocarbon, such as benzene, toluene or xylene; an aliphatic hydrocarbon, such as hexane or heptane; an amide, such as dimethylformamide or dimethylacetamide; a sulphoxide, such as dimethyl sulphoxide; or a sulphone, such as sulpholane. There is no particular limitation on the molar ratio of compound (IX) to the compound R^7X, but we generally prefer to use a slight molar excess of the compound (IX), in order to reduce the risk of protecting the hydroxy group in the side chain at the 2- position. In general, we prefer to employ from 0.8 to 1 mole of the compound R^7X per mole of the compound (IX). The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors.

especially the natures of the starting material, the compound R^7X and the solvent, but we normally prefer a reaction temperature of from 0 to 50°C and a time of from several minutes to several tens of minutes.

The protected chroman alcohol produced by this reaction can, if desired, be isolated and purified, but it may be, and preferably is, converted to the nitrophenoxyalkylchroman compound of formula (X) without intermediate isolation.

Conversion to the compound of formula (X) is effected by reacting the protected compound (IX) with a 4-halonitrobenzene in the presence of a base, such as sodium hydride, in a solvent, such as dimethyl sulphoxide or dimethylformamide. The amount of 4-halonitrobenzene employed is preferably about 2 moles per mole of protected compound (IX). The reaction temperature is preferably from 30 to 100°C and the time required for the reaction is usually from several minutes to several hours.

Step (A3)

The nitro compound of formula (X) thus obtained is reduced in this step to the corresponding amino compound of formula (XI). In the course of or before or after

this reduction, the protecting group R^7 may be allowed to remain as it is, removed or converted to another group (particularly an acyl group, such as an acetyl or benzoyl group).

When deprotection of the compound (X) is desired, this can easily be achieved by reacting the compound (X) with a dilute aqueous acid (such as hydrochloric acid, sulphuric acid or nitric acid) to hydrolyse the protecting group. The reaction is normally carried out in the presence of a solvent, for example: an alcohol, such as methanol, ethanol or propanol; an ether, such as tetrahydrofuran or dioxane; a ketone, such as acetone or methyl ethyl ketone; an organic acid, such as acetic acid or propionic acid; dimethyl sulphoxide; dimethylformamide; or water. Of these, water or an organic acid is preferred. The amount of acid used for hydrolysis is preferably from 0.01 to 5 moles, more preferably from 0.01 to 1 mole, per mole of the compound (X). We prefer to carry out the reaction in the presence of a large molar excess of water or of acetic acid as the solvent. The reaction temperature is preferably from ambient temperature to 100°C and the time required for the reaction is normally from several minutes to about 20 hours.

If it is desired to convert the protecting group

R^7 to another group, particularly an acyl group, this may be achieved by acylation of the deprotected compound obtained as described above. The acylating agent may be an acid halide, such as acetyl chloride or benzoyl chloride, or an acid anhydride, such as acetic anhydride. This reaction is preferably carried out in the presence of an organic amine (such as pyridine or triethylamine) or in the presence of an inorganic base (for example an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide, or an alkali metal carbonate or bicarbonate, such as sodium carbonate, potassium carbonate or sodium bicarbonate). The acylating reaction is preferably carried out in the presence of a solvent, for example: an aliphatic hydrocarbon, such as hexane, cyclohexane, heptane, ligroin or ethylcyclohexane; an aromatic hydrocarbon, such as benzene, toluene or xylene; an organic amine, such as pyridine or triethylamine; a ketone, such as acetone or methyl ethyl ketone; an amide, such as dimethylformamide; a sulphoxide, such as dimethyl sulphoxide; or water. The ratio of the amount of deprotected compound (X) to acylating agent is not particularly critical, however, a slight molar excess of acylating agent is usually preferred, for example from 1 to 1.5 moles of acylating agent per mole of deprotected compound (X). Where an organic amine is employed as the acid-binding agent, it may be employed in any amount

from 1 mole to a large molar excess per mole of the compound of formula (X). Where an inorganic base is employed as the acid-binding agent, it is preferably employed in an amount of from 1 to 10 moles per mole of the compound of formula (X). The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the natures of the starting material and solvent employed, but the reaction is preferably effected at a temperature of from 0 to 100°C for a period of from several minutes to 20 hours.

The nitro compound of formula (X) (which may optionally have been subjected to any of the processes described above) is then reduced to the amino compound of formula (XI). The reduction may be a catalytic reduction process employing hydrogen or reduction with a metal (such as zinc or iron) and an acid (which may be a mineral acid such as hydrochloric acid or sulphuric acid or an organic acid such as acetic acid). Preferably a catalytic reduction process is employed. The catalyst employed for this catalytic reduction is preferably palladium-on-carbon, Raney nickel or platinum oxide, of which palladium-on-carbon is particularly preferred. The hydrogen pressure is preferably from 1 to 100 atmospheres (1.01 to 101 bars), more preferably from 1 to 6 atmospheres (1.01 to 6.06 bars). The reaction is

preferably effected in the presence of a solvent, the nature of which is not critical, provided that it has no adverse effect upon the reaction. Suitable solvents include: alcohols, such as methanol or ethanol; aromatic hydrocarbons, such as benzene or toluene; ethers, such as tetrahydrofuran; organic acids, such as acetic acid; water; or mixtures of any two or more thereof. The reaction conditions, particularly the reaction temperature and time, may vary depending upon a number of factors, particularly the nature of the starting material, the method employed for reduction and the solvent, but the reaction is normally effected at a temperature from ambient to 50°C and the period required for the reaction is generally from several minutes to about 20 hours.

Step (A4)

The 2-(4-aminophenoxyalkyl)chroman derivative of formula (XI), prepared as described in step (A3) above, is diazotized and then subjected to a Meerwein arylation, to give the desired α-halocarboxylic acid compound of formula (IIa). The two reactions are preferably effected sequentially in the same reaction system and under essentially the same conditions.

The diazotization reaction comprises reacting the

amino compound of formula (XI) with a nitrite (such as sodium nitrite) in the presence of an acid, such as hydrochloric acid or hydrobromic acid.

The Meerwein arylation reaction comprises reacting the resulting diazonium compound with acrylic acid, an acrylic acid ester (such as methyl acrylate or ethyl acrylate) or another acrylic acid derivative (such as acrylonitrile or acrylamide) in the presence of a catalytic amount of a cuprous compound (which may be a salt, such as cuprous chloride, or another cuprous compound such as cuprous oxide). The acrylic acid esters are preferred and the preferred cuprous compound is cuprous oxide.

The reactions are preferably effected in the presence of a solvent, the nature of which is not critical, provided that it does not interfere with the reactions. Suitable solvents include: alcohols, such as methanol or ethanol; ketones, such as acetone or methyl ethyl ketone; water; or a mixture of any two or more thereof. The molar ratio of the amino compound of formula (XI) to the acrylic acid or derivative thereof is preferably from 1:1 to 1:15, more preferably from 1:5 to 1:10. The molar ratio of the amino compound (XI) to the cuprous compound is preferably from 1:0.01 to 1:1, more preferably from 1:0.03 to 1:0.3. The reaction

AUSTRALIA

FORM 7

DECLARATION FOR CONVENTION PATENT APPLICATION

(Note: (1) To be signed by the applicant(s), if individual(s). If applicant is a Company, to be signed by a person on its behalf. (2) This is a comprehensive form, and parts inappropriate to a particular application should be cancelled.)

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1960

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

INSTRUCTIONS

(a) Insert No. if available

(b) Insert full name(s) of applicant(s)

(c) Insert title of invention

(d) Insert full name(s) and declarant(s)

(e) Insert address(es) of declarant(s)

In support of the Convention application No. (a) .....

made by (b) SANKYO COMPANY LIMITED

for a patent ~~patent of addition~~ for an invention entitled (c) THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

I/~~We~~ (d) Yoshibumi Kawamura Officer of care of and on behalf of SANKYO COMPANY LIMITED

of (e) 1-6 3-Chome, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan

do solemnly and sincerely declare as follows:—

1. ~~I am the applicant(s) named in the application for the patent/patent of addition~~

(or, in the case of an application by a body corporate)

1. I am/~~We are~~ authorized by the abovementioned applicant(s) for the patent/~~patent of addition~~ to make this declaration on its/their behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date(s) by the following applicant(s) namely:—

(f) Insert country in which first basic application was filed.

(g) Insert date of first basic application.

(h) Insert full name(s) of basic applicant(s)

in (f) Japan on (g) 30th August, 19 83

by (h) SANKYO COMPANY LIMITED

in (f) ..... on (g) 19

by (h) .....

in (f) ..... on (g) 19

by (h) .....

3. ~~I am the actual inventor and the only person named as inventor in the application~~

(or, where a person other than the inventor is the applicant)

(i) Insert full name(s) of actual inventor(s)

(j) Insert address(es) of actual inventor(s)

3. (i) TAKAO YOSHIOKA, EIICHI KITAZAWA and TOMOYUKI KURUMADA all c/o Chemical Research Laboratories; MITSUO YAMAZAKI and KAZUO HASEGAWA, c/o Biological Research Laboratories, all ~~of~~ Sankyo Company Limited, 2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo, Japan

is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows:—

(k) State manner in which applicant(s) derive(s) title from actual inventor(s)

(k) The applicants are assignees of the actual inventors in respect of the invention

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

(b) Signature(s) of declarant(s)

(Note: No attestation or other signature is required)

Declared at Tokyo, JAPAN this 21st day of AUGUST 1984

(b) Yoshibumi Kawamura

Sankyo Company Limited

Yoshibumi Kawamura

Representative Director and President

To: The Commissioner of Patents,
Commonwealth of Australia.

AUSTRALIA

57.0067 08/476,385

M R Sikes

Form 10 5.5.94

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number:
Lodged: 32559/84

Complete Specification—Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: SANKYO COMPANY LIMITED

Address of Applicant: 1-6, 3-chome, Nihonbashi Honcho, Chuo-ku, Tokyo, JAPAN

Actual Inventor: Takao Yoshioka ; Ellchi Kitazawa ; Tomoyuki Karumada; Mitsuo Yamazaki and Kazuo Hasegawa

Address for Service: GRIFFITH HASSEL & FRAZER
71 YORK STREET
SYDNEY, N.S.W. 2000, AUSTRALIA

Complete Specification for the invention entitled: THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

The following statement is a full description of this invention, including the best method of performing it known to me:—

---

* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

14599/78—L

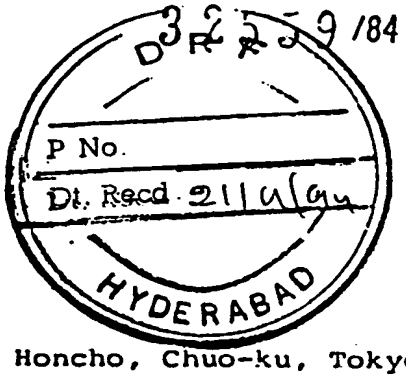
Printed by C. J. THOMPSON, Commonwealth Government Printer, Canberra

570067

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1973

APPLICATION FOR A PATENT



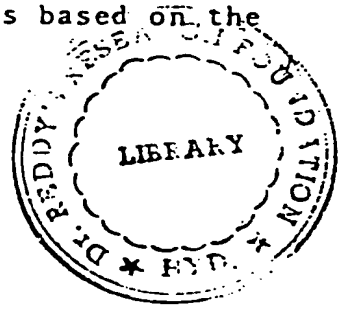
We SANKYO COMPANY LIMITED

of 1-6, 3-chome, Nihonbashi Honcho, Chuo-ku, Tokyo, JAPAN

hereby apply for a grant of a Patent for an invention entitled :

THIAZOLIDINE DERIVATIVES, THEIR PREPARATION AND COMPOSITIONS CONTAINING THEM

which is described in the accompanying complete specification.
This Application is a Convention Application and is based on the Application(s) numbered : 158375/83



for a Patent or similar protection made in Japan

on 30 August 1983

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 5. 1. 88

Our address for service is care of GRIFFITH HASSEL & FRAZER, Patent Attorneys of 71 York Street, Sydney 2000, in the State of New South Wales, Commonwealth of Australia.

Dated this 29th day of August 1984

LODGED AT SUB-OFFICE
30 AUG 1984
Sydney

SANKYO COMPANY LIMITED
By their Patent Attorneys

GRIFFITH HASSEL & FRAZER

APPLICATION ACCEPTED AND AMENDMENTS
ALLOWED 5. 1. 88
TO : THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA